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(54) Title: DOG AND RABBIT MOTILIN RECEPTOR ORTHOLOGS

(57) Abstract: The present invention features polypeptides and nucleic acids related to the dog and rabbit motilin receptor, and uses of such polypeptides and nucleic acids. The dog motilin receptor exon 1 amino acid sequence is provided for by SEQ. ID. NO. 1, the rabbit motilin receptor amino acid sequence is provided for by SEQ. ID. NO. 2, the nucleic acid sequence encoding for exon 1 of the dog motilin receptor is provided for by SEQ. ID. NO. 3, and the nucleic acid sequence encoding for the rabbit motilin receptor is provided for by SEQ. ID. NO. 4.

TITLE OF THE INVENTION

DOG AND RABBIT MOTILIN RECEPTOR ORTHOLOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Serial No. 60/162,264, filed October 29, 1999, hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

The references cited herein are not admitted to be prior art to the claimed invention.

Motilin is a 22 amino acid peptide hormone affecting gastric motility. Motilin has been found to induce smooth muscle contractions in the gastrointestinal tract of different species including humans, cats, rabbits, dogs, and chickens. (Peeters and Depoortere, *Digestive Diseases and Sciences 39*:765-785, 1994; Van Assche, *et al., European Journal of Pharmacology 337*:267-274, 1997; Depoortere and Peters, *American Journal of Physiology 272*:G994 (1997); Kitazawa, *et al., Peptides 16*:1243-1252, 1995; and Itoh, *Peptides 18*:593-608, 1997.)

The effects of motilin include inducing interdigestive (phase III) antrum and duodenal contractions. (Itoh, *Peptides 18*:593-608, 1997; Poitras, in *Gut Peptides: Biochemistry and Physiology*, J. H. Walsh and G. J. Dockray, Eds. (Raven, New York, 1994), pp. 261-304; and Tonini, *Pharmacol. Res.* 33:217-226, 1996.) The antibiotic erythromycin induces similar effects that may be mediated by motilin receptors. (Itoh, *et al., American Journal of Physiology 247*:G688-G694, 1984; and Weber, *et al., American Journal of Gastroenterology 88*:485-490, 1993.) Erythromycin produces side effects including vomiting, nausea, diarrhea and abdominal discomfort. (Tonini, *Pharmacol. Res.* 33:217-226, 1996.)

SUMMARY OF THE INVENTION

The present invention features polypeptides and nucleic acids related to the dog and rabbit motilin receptor, and uses of such polypeptides and nucleic acids. The dog motilin receptor exon 1 amino acid sequence is provided for by SEQ. ID. NO. 1, the rabbit motilin receptor amino acid sequence is provided for by SEQ. ID. NO. 2, the nucleic acid sequence encoding for exon 1 of the dog motilin receptor is provided for by SEQ. ID. NO. 3,

and the nucleic acid sequence encoding for the rabbit motilin receptor is provided for by SEQ. ID. NO. 4.

Polypeptides related to the dog or rabbit motilin receptor contain a region of at least 9 contiguous amino acids that are present in the dog or rabbit motilin receptor. Such polypeptides may contain additional regions including regions present, or not present, in the dog or rabbit motilin receptor.

Nucleic acids related to the dog or rabbit motilin receptor contain a region of at least 18 contiguous nucleotides that is present in the dog or rabbit motilin receptor nucleic acid or the complement thereof. Such nucleic acids may contain additional regions including regions present, or not present, in the dog or rabbit motilin receptor nucleic acid.

Thus, a first aspect of the present invention describes a purified polypeptide comprising a unique amino acid region of a dog or rabbit motilin receptor. The unique region is at least 9 amino acids in length.

A "unique amino acid region" is a region of contiguous amino acids present in SEQ. ID. NOs. 1 or 2 that is not present in SEQ. ID. NOs. 5 or 6. SEQ. ID. NO. 5 is a human motilin receptor amino acid sequence and SEQ. ID. NO. 6 is an amino acid sequence for *Spheroides nephelus* 75E7. The unique region may contain segments of contiguous amino acids present in SEQ. ID. NOs. 5 or 6 smaller than the indicated unique region size.

A "purified polypeptide" represents at least 10% of the total protein present in a sample or preparation. In preferred embodiments, the purified polypeptide represents at least about 50%, at least about 75%, or at least about 95% of the total protein in a sample or preparation. Reference to "purified polypeptide" does not require that the polypeptide has undergone any purification and may include, for example, chemically synthesized polypeptide that has not been purified.

Another aspect of the present invention describes a purified nucleic acid comprising a nucleotide sequence encoding for a unique amino acid region from the dog or rabbit motilin receptor or the complement thereof. The encoded for region is at least 9 amino acids in length.

A "purified nucleic acid" represents at least 10% of the total nucleic acid present in a sample or preparation. In preferred embodiments, the purified nucleic acid represents at least about 50%, at least about 75%, or at least about 95% of the total nucleic acid a sample or preparation. Reference to "purified nucleic acid" does not require that the nucleic acid has undergone any purification and may include, for example, chemically synthesized nucleic acid that has not been purified.

Another aspect of the present invention describes a purified nucleic acid comprising a unique nucleotide sequence region of a dog or rabbit motilin receptor nucleic acid sequence. The unique nucleotide sequence region is at least 18 nucleotides in length.

A "unique nucleotide sequence region" is a region that comprises at least 18 contiguous nucleotides of SEQ. ID. NOs. 3 or 4 that is not present in SEQ. ID. NOs. 7 or 8. SEQ. ID. NO. 7 is the nucleotide sequence encoding for a human motilin receptor and SEQ. ID. NO. 8 is the nucleotide sequence encoding for *Spheroides nephelus* 75E7. The unique region may contain segments of contiguous nucleotides present in SEQ. ID. NOs. 7 or 8 smaller than the indicated unique region size.

Another aspect of the present invention describes an expression vector. The expression vector comprises a recombinant nucleotide sequence encoding for a unique amino acid region of a dog or rabbit motilin receptor.

A "recombinant nucleotide sequence" is a sequence that is present on a nucleic acid containing one or more nucleic acid regions not naturally associated with that sequence. Examples of such regions that may be present include one or more regulatory elements not naturally associated with the sequence, viral elements, and selectable markers.

Another aspect of the present invention describes a recombinant cell comprising an expression vector encoding for a unique amino acid region of a dog or rabbit motilin receptor. The expression vector contains a promoter that is functionally coupled to nucleic acid encoding for the unique region and is recognized by an RNA polymerase present in the cell.

Another aspect of the present invention describes a recombinant cell made by introducing an expression vector encoding for a unique amino acid region of a dog or rabbit motilin receptor into a cell. The expression vector can be used to insert the dog or rabbit nucleic acid into the genome of the host, or can exist as an autonomous piece of nucleic acid.

Another aspect of the present invention describes a method of measuring the ability of a compound to effect motilin receptor activity. The method involves providing the compound to a recombinant cell expressing a functional motilin receptor containing a unique dog or rabbit amino acid region from a recombinant nucleic acid and measuring motilin receptor activity. Preferably, the recombinant nucleic acid is present on an expression vector.

Another aspect of the present invention describes a method of producing a motilin receptor polypeptide. The method involves the step of growing a recombinant cell able to express a dog or rabbit motilin receptor polypeptide under conditions wherein the polypeptide is expressed from an expression vector.

Other features and advantages of the present invention are apparent from the additional descriptions provided herein including the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a comparison of the protein sequence for the dog motilin receptor exon 1 (SEQ. ID. NO. 1), the rabbit motilin receptor (SEQ. ID. NO. 2), the human motilin receptor (SEQ. ID. NO. 5) and *Spheroides nephelus* 75E7 (SEQ. ID. NO. 6).

Figures 2A-2C illustrate a comparison of the DNA sequence encoding for the dog motilin receptor exon 1 (SEQ. ID. NO. 3), the rabbit motilin receptor (SEQ. ID. NO. 4), the human motilin receptor (SEQ. ID. NO. 7) and *Spheroides nephelus* 75E7 (SEQ. ID. NO. 8).

DETAILED DESCRIPTION OF THE INVENTION

The present invention features polypeptides and nucleic acids related to the dog and rabbit motilin receptor. Preferred polypeptides contain an amino acid region not present in the human motilin receptor or *Spheroides nephelus* 75E7. Preferred nucleic acids contain a nucleotide region not present in nucleic acid encoding for the human motilin receptor or *Spheroides nephelus* 75E7.

The amino acid sequence and encoding DNA sequence for two alternatively spliced forms of the human motilin receptor (MTL-R1 and MTL-R2) are described by Feighner, *et al.*, *Science 284*:2184-2188, 1999 (not admitted to be prior art to the claimed invention). Additionally, an amino acid sequence for genomic DNA encoding for "GPR38" is described by McKee, *et al.*, *Genomics 46*:426-434, 1997. Feighner, *et al.*, identifies GPR38 as the motilin receptor and indicates the presence of an intron.

The *Spheroides nephelus* gene 75E7 has a high level of homology to the human motilin receptor. The protein sequence of 75E7 is 54% identical to human motilin receptor (MTL-R1) and contains a similar exon-intron structure. (Feighner, *et al.*, *Science 284*:2184-2188, 1999.)

A preferred use of dog and rabbit motilin receptor polypeptides and nucleic acids is in an *in vitro* functional assay that measures whether a compound acts differently at

the dog or rabbit receptor than at the human receptor. Such an assay can be used to help evaluate whether a dog or rabbit model provides a useful test system in looking for a human therapeutic compound.

Therapeutic uses of compounds active at the motilin receptor include the treatment gastrointestinal diseases and disorders such as gastric motility disorders (intrinsic myopathies or neuropathy), gastroparesis, irritable bowel syndrome, and diarrhea. Additionally, compounds active at the motilin receptor can be used as a research tool for studying motilin receptor activity.

MOTILIN RECEPTOR RELATED POLYPEPTIDES

Polypeptides related to the dog and rabbit polypeptide contain a unique dog or rabbit amino acid region. In addition to the unique amino acid region, regions that may, or may not, be related to the dog or rabbit motilin receptor polypeptide may be present in the polypeptides. Such polypeptides have a variety of uses, such as providing a component of a functional motilin receptor; being used as an immunogen to produce antibodies binding to the dog or rabbit motilin receptor; being used as a target to identify compounds binding to the motilin receptor; and/or being used in assays to measure the ability of a compound to effect motilin receptor activity.

Unique dog and rabbit amino acid regions can readily be identified based on a comparison of the dog and rabbit motilin receptor sequences described herein, with the human motilin receptor and the *Spheroides nephelus* 75E7 protein sequences. Such a sequence comparison is illustrated in Figure 1. Examples of unique dog amino acid regions include the following: GPGNSSDGA (SEQ. ID. NO. 9); VCLGLFAVGV (SEQ. ID. NO. 10); ALLSSRRRA (SEQ. ID. NO. 11); APFFFLVGVEQDAGG (SEQ. ID. NO. 12); and CLCVLYGRI (SEQ. ID. NO. 13). Examples of unique rabbit amino acid regions include the following: DPAVFAAPDR (SEQ. ID. NO. 14); NGTVPLDPS (SEQ. ID. NO. 15); SPAPASPPSGPG (SEQ. ID. NO. 16); RRLLRESRAG (SEQ. ID. NO. 17); and SGVCGSRGPEQD (SEQ. ID. NO. 18).

The definition of unique amino acid region is with respect to human motilin receptor and *Spheroides nephelus* 75E7 protein sequences. Thus, a unique amino acid region may be present in a motilin receptor sequence from one or more species other than the human motilin receptor or *Spheroides nephelus* 75E7 protein sequence, or in a non-motilin receptor sequence. For example, SEQ. ID. NO. 10 is present in both the dog and rabbit motilin receptor.

In different embodiments a dog or rabbit motilin receptor related polypeptide comprises or consists of a unique amino acid region at least 18, at least 27, or at least 54, bases in length. Preferably, the dog or rabbit motilin receptor related polypeptide comprises or consists of the amino acid sequence of SEQ. ID. NO. 1 or SEQ. ID. NO. 2.

Polypeptides can be produced using standard techniques including those involving chemical synthesis and those involving biochemical synthesis. Techniques for chemical synthesis of polypeptides are well known in the art. (See *e.g.,* Vincent, in *Peptide and Protein Drug Delivery*, New York, N.Y., Dekker, 1990.)

Biochemical synthesis techniques for polypeptides are also well known in the art. Such techniques employ a nucleic acid template for polypeptide synthesis. The genetic code providing the sequences of nucleic acid triplets coding for particular amino acids is well known in the art. (*See, e.g.*, Lewin *GENES IV*, p. 119, Oxford University Press, 1990.) Examples of techniques for introducing nucleic acid into a cell and expressing the nucleic acid to produce protein are provided in references such as Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998, and Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual,* 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.

Functional Motilin Receptor Derivatives

Functional motilin receptors can bind motilin and transduce an intracellular signal. Functional motilin receptors include the dog and rabbit motilin receptors, and receptors having motilin receptor activity that contain a unique dog or rabbit amino acid region as a component.

Starting with a motilin receptor obtained from a particular source, derivatives can be produced having motilin receptor activity. Such derivatives include polypeptides with amino acid substitutions, additional and deletions. Changes made to produce functional derivatives should be made outside of the motilin-binding domain and in a manner not altering the tertiary structure. The ability of a polypeptide to have motilin receptor activity can be confirmed using techniques such as those measuring G-protein activity.

The sequence comparison provided in Figure 1 illustrates amino acids that vary between the human, dog, and rabbit motilin receptors. Such variable amino acids are good targets for alterations.

Additionally, amino acids are classified into certain types based on the structure of their R-groups. Substituting different amino acids within a particular group, such

as substituting valine for leucine, arginine for lysine, and asparagine for glutamine may not cause a change in functionality of the polypeptide.

Motilin Antibodies

Antibodies recognizing a dog or rabbit motilin receptor polypeptide can be produced using a polypeptide of SEQ. ID. NO. 1, SEQ. ID. NO. 2, or a fragment thereof as an immunogen. Fragments should be at least 9 amino acids in length and preferably consist of a unique amino acid region.

Antibodies to the motilin receptor have different uses such as being used to identify the presence of motilin receptor polypeptides and for isolating motilin receptor polypeptides. Examples of techniques for producing and using antibodies are described in Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998, Harlow, *et al., Antibodies, A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988, and Kohler, *et al., Nature 256*:495-497, 1975.

Binding Assays

Assays measuring the ability of a compound to bind the dog or motilin receptor can be performed using a polypeptide of SEQ. ID. NO. 1, SEQ. ID. NO. 2, or a fragment thereof as a target. Fragments should be at least 9 amino acids in length and contain a site to which either an agonist, antagonist, or allosteric modulator binds. Different types of assay formats can be employed including competitive and non-competitive assays.

Compounds identified as binding to a full-length receptor or a receptor fragment can be used to determine the locus of a binding site by testing out the ability of the compound to bind to smaller length fragments. For example, motilin binds to the motilin receptor and labeled motilin can be used to identify that portion of the receptor to which motilin binds. Fragments identified as containing a compound binding site can be used to test for additional compounds that bind to the binding site.

Preferred polypeptide fragments used in a binding assay consist of a unique amino acid region. However, fragments containing additional amino acid sequences can be employed, for example, to facilitate attachment to a column.

Binding assays can be performed using individual compounds or preparations containing different compounds. A preparation containing different compounds wherein one or more compounds bind to the motilin receptor can be divided into smaller groups to

identify compound(s) binding to the motilin receptor. In an embodiment of the present invention a test preparation containing at least 10 compounds is used in a binding assay.

Binding assays can be performed using recombinantly produced motilin receptor polypeptides present in different environments. Such environments include, for example, cell extracts and purified cell extracts containing the motilin receptor polypeptide expressed from recombinant nucleic acid; and the use of a purified motilin receptor polypeptide produced by recombinant means which is introduced into a different environment.

Functional Assays

Assays involving functional dog or rabbit motilin receptors can be employed to select for compounds active at the motilin receptor and to evaluate the ability of a compound to effect receptor activity. Motilin receptor activity can be measured using different techniques such as detecting a change in the intracellular conformation of the motilin receptor, measuring G-protein activity, or measuring the level of intracellular messengers.

Recombinantly expressed motilin receptor polypeptides can be used to facilitate determining whether a compound is active at the motilin receptor or another receptor. For example, the motilin receptor can be expressed by an expression vector in a cell line such as HEK 293, COS 7, and CHO not normally expressing the receptor, wherein the same cell line without the expression vector or with an expression vector not encoding for a motilin receptor can act as a control.

Motilin receptors appear to activate the phospholipase C signal transduction pathway. Activity of the phospholipase C signal transduction pathway can be measured using standard techniques such as those measuring intracellular Ca^{2+}. Examples of techniques well known in the art that can be employed to measure Ca^{2+} include the use of dyes such as Fura-2 and the use of Ca^{2+}-bioluminescent sensitive reporter proteins such as aequorin. An example of a cell line employing aequroin to measure G protein activity is HEK293/aeq17. (Button, *et al., Cell Calcium 14*:663-671, 1993, and Feighner, *et al., Science 284*:2184-2188, 1999, both of which are hereby incorporated by reference herein.)

Chimeric receptors containing a motilin binding region functionally coupled to polypeptides from other G protein can also be used to measure motilin receptor activity. Such chimeric receptors preferably contain at least one unique dog or rabbit amino acid region. A chimeric motilin receptor contains an N-terminal extracellular domain; a

transmembrane domain made up of transmembrane regions, extracellular loop domains, and intracellular loop domains; and an intracellular carboxy terminus. Preferred chimerics contain the extracellular domain of a motilin dog or rabbit receptor.

The specificity of G protein coupling is determined by intracellular domain(s). A chimeric motilin receptor can be produced to functionally couple to a particular G protein such as a Gq protein or a Gi protein. Such signal swapping allows for the detection of motilin receptor activity by measuring Gq or Gi activity. Techniques for producing chimeric receptors and measuring G protein coupled responses are provided for in, for example, International Application Number WO 97/05252, and U.S. Patent Number 5,264,565, both of which are hereby incorporated by reference herein.

Functional assays can be performed using individual compounds or preparations containing different compounds. A preparation containing different compounds where one or more compounds affect motilin receptor activity can be divided into smaller groups of compounds to identify the compound(s) affecting motilin receptor activity. In an embodiment of the present invention a test preparation containing at least 10 compounds is used in a functional assay.

Functional assays can be performed using recombinantly produced motilin receptor polypeptides present in different environments. Such environments include, for example, cell extracts, and purified cell extracts, containing the motilin receptor polypeptide expressed from recombinant nucleic acid; and the use of a purified motilin receptor polypeptide produced by recombinant means which is introduced into a different environment.

MOTILIN RECEPTOR RELATED NUCLEIC ACID

Nucleic acids related to the dog and rabbit motilin receptor nucleic acid contain a unique dog or rabbit nucleotide sequence region. Such nucleic acids have a variety of uses, such as being used as a hybridization probe or PCR primer to identify the presence of dog or rabbit motilin nucleic acid; being used as a hybridization probe or PCR primer to identify nucleic acid encoding for receptors related to the motilin receptor from different sources; and/or being used for recombinant expression of dog or rabbit motilin receptor polypeptide.

Unique dog and rabbit nucleic acid regions can readily be identified based on a comparison of the dog and rabbit motilin receptor nucleic acid sequences described herein,

with the human motilin receptor and the *Spheroides nephelus* 75E7 nucleic acid sequences. Such a sequence comparison is illustrated in Figure 2.

Examples of unique dog nucleic acid regions include the following:

GGCCCCGGGAACAGCAGCGACGGCGCG (SEQ. ID. NO. 19);

GGCCGTGTGCCTGGGCCT (SEQ. ID. NO. 20);

CGCGCGCTGCTGTCCCGG (SEQ. ID. NO. 21);

AGGACGCGGGCGGCCCCG (SEQ. ID. NO. 22); and

CCGCGAGCTGCGGAGGCG (SEQ. ID. NO. 23).

Examples of unique rabbit nucleic acid regions include the following:

TTCGGCCGGGCCCTTCTTCTTT (SEQ. ID. NO. 24);

GGTCTTCGCGGCCCCGGA (SEQ. ID. NO. 25);

CGGTACTGTGCCGCTGGA (SEQ. ID. NO. 26);

GCTTTTCTACCTGAGTGCGTCC (SEQ. ID. NO. 27); and

CGAGCGGGGCCCAGTGGTG (SEQ. ID. NO. 28).

The guidance provided in the present application can be used to obtain the nucleic acid sequence encoding for the full-length dog motilin receptor, to obtain nucleic acids encoding for motilin receptors from additional sources, and to artificially produce a motilin receptor. Obtaining nucleic acids encoding for a motilin receptor from different sources is facilitated using sets of degenerative probes and primers and by the proper selection of hybridization conditions. Sets of degenerative probes and primers are produced taking into account the degeneracy of the genetic code. Adjusting hybridization conditions is useful for controlling probe or primer specificity to allow for hybridization to nucleic acids having similar sequences.

Techniques employed for hybridization detection and PCR cloning are well known in the art. Nucleic acid detection techniques are described, for example, in Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual,* 2nd Edition, Cold Spring Harbor Laboratory Press, 1989. PCR cloning techniques are described, for example, in White, *Methods in Molecular Cloning,* volume 67, Humana Press, 1997.

Motilin receptor probes and primers can be used to screen nucleic acid libraries containing, for example, genomic DNA or cDNA. Such libraries are commercially available, and can be produced using techniques such as those described in Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998.

Starting with a particular motilin receptor amino acid sequence and the known degeneracy of the genetic code, a large number of different encoding nucleic acid sequences

can be obtained. The degeneracy of the genetic code arises because almost all amino acids are encoded for by different combinations of nucleotide triplets. The translation of a particular codon into a particular amino acid is well known in the art (*see, e.g.*, Lewin *GENES IV*, p. 119, Oxford University Press, 1990). Amino acids are encoded for by codons as follows:

A=Ala=Alanine: codons GCA, GCC, GCG, GCU
C=Cys=Cysteine: codons UGC, UGU
D=Asp=Aspartic acid: codons GAC, GAU
E=Glu=Glutamic acid: codons GAA, GAG
F=Phe=Phenylalanine: codons UUC, UUU
G=Gly=Glycine: codons GGA, GGC, GGG, GGU
H=His=Histidine: codons CAC, CAU
I=Ile=Isoleucine: codons AUA, AUC, AUU
K=Lys=Lysine: codons AAA, AAG
L=Leu=Leucine: codons UUA, UUG, CUA, CUC, CUG, CUU
M=Met=Methionine: codon AUG
N=Asn=Asparagine: codons AAC, AAU
P=Pro=Proline: codons CCA, CCC, CCG, CCU
Q=Gln=Glutamine: codons CAA, CAG
R=Arg=Arginine: codons AGA, AGG, CGA, CGC, CGG, CGU
S=Ser=Serine: codons AGC, AGU, UCA, UCC, UCG, UCU
T=Thr=Threonine: codons ACA, ACC, ACG, ACU
V=Val=Valine: codons GUA, GUC, GUG, GUU
W=Trp=Tryptophan: codon UGG
Y=Tyr=Tyrosine: codons UAC, UAU

In different embodiments dog or rabbit motilin receptor related nucleic acid comprises or consists of a unique nucleic acid region at least 27 or at least 54 bases in length. Preferably, the dog or rabbit motilin receptor related nucleic acid comprises or consists of the nucleic acid sequence of SEQ. ID. NO. 3 or SEQ. ID. NO. 4.

Nucleic acid having a desired sequence can be synthesized using chemical and biochemical techniques. Examples of chemical techniques are described in Ausubel, *Current Protocols in Molecular Biology*, John Wiley, 1987-1998, and Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.

Biochemical synthesis techniques involve the use of a nucleic acid template

and appropriate enzymes such as DNA and/or RNA polymerases. Examples of such techniques include *in vitro* amplification techniques such as PCR and transcription based amplification, and *in vivo* nucleic acid replication. Examples of suitable techniques are provided by Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998, Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual,* 2nd Edition, Cold Spring Harbor Laboratory Press, 1989, and Kacian, *et al.*, U.S. Patent No. 5,480,784.

Motilin Receptor Probes

Detection probes for the dog or rabbit motilin receptor preferably contain a unique dog or rabbit nucleic acid region, or the complement thereof. Such probes can contain additional nucleic acid that may, or may not, be complementary to dog or rabbit motilin receptor nucleic acid. Preferably, additional nucleic acid that is present has a particular purpose such as providing for increased specificity, being a reporter sequence, or being a capture sequence. However, additional nucleic acid need not have a particular purpose.

Probes for the motilin receptor can specifically hybridize to motilin receptor target nucleic acid under appropriate hybridization conditions (*i.e.*, distinguish target nucleic acid from one or more non-target nucleic acid molecules). A preferred non-target nucleic acid is either nucleic acid encoding for the human motilin receptor or the complement thereof. Hybridization occurs through complementary nucleotide bases present on the probe and motilin receptor nucleic acid. Hybridization conditions determine whether two molecules have sufficiently strong interactions with each other to form a stable hybrid.

Probes are composed of nucleic acids or derivatives thereof such as modified nucleic acid and peptide nucleic acid. Modified nucleic acid includes nucleic acid with one or more altered sugar groups, altered internucleotide linkages, and/or altered nucleotide purine or pyrimidine bases. References describing modified nucleic acid include WO 98/02582, U.S. Patent No. 5,859,221 and U.S. Patent No. 5,852,188, each of which are hereby incorporated by reference herein.

The degree of interaction between two molecules that hybridize together is reflected by the Tm of the produced hybrid. The higher the Tm the stronger the interactions and the more stable the hybrid. Tm is effected by numerous factors well known in the art such as the degree of complementarity, the type of complementary bases present (*e.g.*, A-T hybridization versus G-C hybridization), the structure of the nucleic acid backbones, and

solution components. *E.g.*, Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.

Stable hybrids are formed when the Tm of a hybrid is greater than the temperature employed under a particular set of hybridization assay condition. The degree of specificity of a probe can be varied by adjusting the hybridization stringency conditions. Detecting probe hybridization is facilitated through the use of a detectable label. Examples of detectable labels include luminescent, enzymatic, and radioactive labels.

Examples of stringency conditions are provided in Sambrook, *et al.*, in *Molecular Cloning, A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989. An example of high stringency conditions is as follows: Prehybridization of filters containing DNA is carried out for 2 hours to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 μg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hours at 65°C in prehybridization mixture containing 100 μg/ml denatured salmon sperm DNA and 5-20 X 10^6 cpm of ^{32}P-labeled probe. Washing of filters is done at 37°C for 1 hour in a solution containing 2X SSC, 0.1% SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 minutes before autoradiography. Other procedures using conditions of high stringency would include, for example, either a hybridization step carried out in 5X SSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

Recombinant Expression

Motilin receptor related polypeptides can be expressed from recombinant nucleic acid in a suitable host or in a test tube using a translation system. Recombinantly expressed motilin receptor polypeptides are preferably used in assays to screen for compounds that bind to the motilin receptor and modulate the activity of the receptor.

Preferably, expression is achieved in a host cell using an expression vector. An expression vector contains recombinant nucleic acid encoding for a desired polypeptide along with regulatory elements for proper transcription and processing. The regulatory elements that may be present include those naturally associated with the recombinant nucleic acid and exogenous regulatory elements not naturally associated with the recombinant nucleic acid. Exogenous regulatory elements such as an exogenous promoter can be useful for expressing recombinant nucleic acid in a particular host.

Generally, the regulatory elements that are present include a transcriptional promoter, a ribosome binding site, a terminator, and an optionally present operator. Another preferred element is a polyadenylation signal providing for processing in eukaryotic cells. Preferably, an expression vector also contains an origin of replication for autonomous replication in a host cell, a selectable marker, a limited number of useful restriction enzyme sites, and a potential for high copy number. Examples of expression vectors are cloning vectors, modified cloning vectors, specifically designed plasmids and viruses.

Expression vectors that can be used to provide suitable levels of polypeptide expression in different hosts are well known in the art. Mammalian expression vectors well known in the art include pcDNA3 (Invitrogen), pMC1neo (Stratagene), pXT1 (Stratagene), pSG5 (Stratagene), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), pSV2-dhfr (ATCC 37146), pUCTag (ATCC 37460), pCI-neo (Promega) and lambda.ZD35 (ATCC 37565). Bacterial expression vectors well known in the art include pET11a (Novagen), lambda gt11 (Invitrogen), pcDNAII (Invitrogen), and pKK223-3 (Pharmacia). Fungal cell expression vectors well known in the art include pYES2 (Invitrogen), Pichia expression vector (Invitrogen). Insect cell expression vectors well known in the art include Blue Bac III (Invitrogen).

Recombinant host cells may be prokaryotic or eukaryotic. Examples of recombinant host cells include the following: bacteria such as *E. coli*; fungal cells such as yeast; mammalian cells such as human, bovine, porcine, monkey and rodent; and insect cells such as Drosophila and silkworm derived cell lines. Commercially available mammalian cell lines include L cells L-M(TK.sup.-) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26) and MRC-5 (ATCC CCL 171).

Expression vectors may be introduced into host cells using standard techniques. Examples of such techniques include transformation, transfection, lipofection, protoplast fusion, and electroporation.

Motilin receptor nucleic acid can be expressed in a cell without the use of an expression vector employing, for example, synthetic mRNA or native mRNA. Additionally, mRNA can be translated in various cell-free systems such as wheat germ extracts and

reticulocyte extracts, as well as in cell based systems, such as frog oocytes. Introduction of mRNA into cell based systems can be achieved, for example, by microinjection.

EXAMPLES

Examples are provided below to further illustrate different features and advantages of the present invention. The examples also illustrate useful methodology for practicing the invention. These examples do not limit the claimed invention.

Example 1: Cloning of the Rabbit Motilin Receptor

A rabbit motilin receptor was identified and cloned from a λDashII genomic library (Stratagene, La Jolla, CA) by screening with a human MTLR probe (exon I & II, GPR38; McKee, *et al., Genomics 46*:426-434, 1977, hereby incorporated by reference herein). Hybridization was performed using reduced-stringency conditions as described below.

1.1×10^6 plaque forming units (pfu) were plated on *E. coli* XLBlue MRA (P2) and transferred to nylon membranes (NEF-978A; NEN, Boston, MA). Duplicate membranes were incubated overnight at 30°C in prehybridization solution (50% formamide, 2X Denhardt's, 5X SSPE, 0.1% SDS, 100 μg/ml salmon sperm DNA) followed by overnight incubation in hybridization solution (50% formamide, 2X Denhardt's, 5X SSPE, 0.1% SDS, 10% dextran sulfate, 100 μg/ml salmon sperm DNA) with 1×10^6 cpm/ml labeled probe and final wash conditions of 1X SSC at 55°C. A clone was identified after two rounds of screening and sequenced with BIG DYE terminator cycle sequencing Ready Reactions (Perkin Elmer, Foster City, CA) on a 377 ABI Prism cycle sequencer (Perkin Elmer, Foster City, CA).

To generate a contiguous open reading frame (ORF) for the rabbit motilin receptor, overlapping PCR was performed on exons I and II. PCR products for exons I and II were produced each containing a small portion of the other exon. The primers for exon I, SEQ. ID. NO. 29 (5' gggcccgaattcgccgccATGGGCAGCCCCTGGAACGGCAGC) and SEQ. ID. NO. 30 (5'GGCCAGAACCACCACCAGCAGGACGCGGACGGTCTG), contained an EcoRI site and a "GCC GCC" Kozac sequence. The primers for exon II, SEQ. ID. NO. 31 (5'GTCCGCGTCCTGCTGGTGGTGGTTCTGGCCTTTATAGTG) and SEQ. ID. NO. 32 (5'agtttagcggccgcCTATGCAGCCGTCTTTGTGTTAGC3'), contained a NotI site. The rabbit motilin ORF was then generated from exon I and II templates and primers SEQ. ID. NO. 29 and SEQ. ID. NO. 32.

An Advantage cDNA PCR kit (Clontech, Palo Alto, CA) was used in the PCR reactions generally following manufacture instructions. Two exceptions were the addition of 5% DMSO to the PCR reactions and PCR cycling as follows: 1) 94°C for 1 minute, 2) 5 cycles of 94°C for 30 seconds, 72°C for 3 minutes, 3) 5 cycles of 94°C for 30 seconds, 70°C for 3 minutes, 4) 20 cycles of 94°C for 30 seconds, 68°C for 3 minutes. The rabbit motilin ORF fragment was digested with EcoRI and NotI, gel-purified, ligated into pcDNA3 vector and transformed into SCS1 *E. coli* (Stratagene, La Jolla, CA).

Example 2: Cloning of the Dog Motilin Receptor Exon 1

A dog motilin receptor exon was identified and cloned by screening the canine lambda FixII genomic library (Stratagene, La Jolla , CA) with the human MTLR probe (see Example 1). Using techniques illustrated herein, such as those described in Example 1, the full-length clone can readily be obtained.

Hybridization was performed using reduced-stringency conditions. 1.2×10^6 phage plaques of the once amplified library were plated onto *E. coli* XL1-Blue MRA at 30,000 pfu per 150 mm plate. The phage were transferred onto nylon hybridization transfer membranes (NEN, Boston, MA) in duplicate, denatured, neutralized, washed and probed with random primed (Prime-It II kit, Stratagene, La Jolla, CA) P^{32}dCTP labeled human MTLR exon I and exon II probes. The membranes were prehybridized (50% formamide, 2X Denhardt's, 5X SSPE, 0.1% SDS, 100 µg/mL salmon sperm DNA) for two hours followed by overnight hybridization (50% formamide, 2X Denhardt's, 5X SSPE, 10% dextran sulfate, 0.1% SDS, 100 µg/mL salmon sperm DNA), shaking in a 32°C incubator with probe at 1×10^6 cpm/mL. The filters were washed in 4X SSC, 0.1% SDS solution at 23°C followed by 2X SSC, 0.1% SDS at 42°C and finally 1X SSC, 0.1% SDS at 55°C.

After two rounds of plaque purification seven clones were isolated. Lamba DNA was isolated from the seven clones using a liquid lysate preparation. The indicator strain XL1-Blue MRA was lysed with eluted phage and cell debris spun down. The liquid phage stock was treated with RNaseA at 38 µg/mL, 37°C for 30 minutes and PEG-precipitated (10% PEG8000/1M NaCl in SM buffer) overnight at 4°C. Pelleted phage DNA was proteinase K treated (50 µg/mL, 68°C, 15 minutes). This was followed by phenol/chloroform and chloroform extractions and ethanol precipitation.

Lambda DNA was spooled out with a sterile pipet tip, washed with 70% ethanol and resuspended in sterile water. Each DNA was digested with a band of restriction enzymes (BamHI, EcoRI, NotI, PstI, SmaI and XbaI), electrophoresed on 1% Seakem GTG

1X TAE agarose gel, southern blotted and probed with human MTLR exon I and II probes as described above. Hybridizing bands were subcloned and sequenced on ABI 377 automated sequencer using Big Dye terminator premix (Perkin Elmer, Foster City, CA). Sequence information obtained was then analyzed using the Sequencer program. Of these, a 2kB NotI fragment from lambda DNA 35 contained the largest fragment of dog MTLR encoding exon I, the splice junction, and intronic sequence.

Example 3: Dog and Rabbit Motilin Receptor Sequences

The nucleotide and amino acid sequences for SEQ. ID. NOs. 1, 2, 3, and 4 are provided as follows:

SEQ. ID. NO. 1

MGGPGNSSDGAEGAQLPCDERLCSPFPLGALVPVTAVCLGLFAVGVSGNLVTVLLIG
RYRDMRTTTNLYLGSMAVSDLLILLGLPLDLYRLWRSRPWVFGQLLCRLSLYLGEG
CTYATLLHVTALSVERYLAVCRPLRARALLSRRRARALIAALWAVALLSAAPFFFLV
GVEQDAGGPGLNGSARLARAPSPPPGPEAALFSRECRPSPSQLGALRVMLWVTTAYF
FLPFLCLCVLYGRIGRELRRRRGPLRGRAASGRERGHRQAVRVL

SEQ. ID. NO. 2

MGSPWNGSDGPEDAREPPWAALPPCDERRCSPFPLGTLVPVTAVCLGLFAVGVSGN
VVTVLLIGRYRDMRTTTNLYLGSMAVSDLLILLGLPFDLYRLWRSRPWVFGQLLCRL
SLYVGEGCTYASLLHMTALSVERYLAICRPLRARVLVTRRRVRALIAALWAVALLS
AGPFFFLVGVEQDPAVFAAPDRNGTVPLDPSSPAPASPPSGPGAEAAALFSRECRPSR
AQLGLLRVMLWVTTAYFFLPFLCLSILYGLIARQLWRGRGPLRGPAATGRERGHRQT
VRVLLVVVLAFIVCWLPFHVGRIIYINTQDSRMMYFSQYFNIVALQLFYLSASINPILY
NLISKKYRAAARRLLRESRAGPSGVCGSRGPEQDVAGDTGGDTAGCTETSANTKTA
A

SEQ. ID. NO. 3

ATGGGCGGCCCCGGGAACAGCAGCGACGGCGCGGAGGGCGCGCAGCTGCCGTG
CGACGAGCGCCTGTGCTCGCCCTTCCCCCTGGGGGCGCTGGTGCCGGTGACGGCC
GTGTGCCTGGGCCTGTTCGCCGTCGGCGTGAGCGGCAACCTGGTGACGGTGCTGC
TGATCGGCCGCTACCGCGACATGCGCACCACCACCAACCTGTACCTGGGCAGCA
TGGCCGTGTCCGACCTGCTCATCCTGCTGGGGCTGCCCCTCGACCTGTACCGCCT

GTGGCGCTCGCGGCCCTGGGTGTTCGGGCAGCTGCTGTGCCGCCTGTCGCTGTAC
CTGGGCGAGGGCTGCACCTACGCCACGCTGCTGCACGTGACGGCGCTGAGCGTC
GAGCGCTACCTGGCCGTGTGCCGCCCGCTCCGCGCCCGCGCGCTGCTGTCCCGGC
GCCGCGCCCGCGCGCTCATCGCGGCGCTCTGGGCCGTGGCGCTGCTGTCGGCCGC
GCCCTTCTTCTTCCTGGTGGGCGTCGAGCAGGACGCGGGCGGCCCCGGCCTCAAC
GGCAGCGCGCGGCTGGCGCGGGCGCCCTCCCCGCCGCCGGGGCCCGAGGCGGCG
CTCTTCAGCCGGGAGTGCCGGCCCAGCCCGTCGCAGCTGGGCGCGCTGCGCGTC
ATGCTCTGGGTCACCACCGCCTACTTCTTCCTGCCCTTCCTGTGCCTCTGCGTCCT
GTACGGGCGCATCGGCCGCGAGCTGCGGAGGCGCCGGGGGCCGCTGCGGGGCC
GGGCCGCCTCGGGGCGCGAGCGGGGCCACCGCCAGGCCGTCCGCGTGCTG

SEQ. ID. NO. 4

ATGGGCAGCCCCTGGAACGGCAGCGACGGCCCCGAGGACGCGCGGGAGCCGCC
GTGGGCCGCGCTGCCGCCGTGCGATGAGCGCCGCTGCTCGCCCTTCCCCTTGGGC
ACGCTGGTGCCTGTGACGGCCGTGTGCCTGGGCCTGTTCGCCGTCGGGGTGAGCG
GCAACGTGGTGACCGTGCTGCTGATCGGGCGCTACCGGGACATGCGGACCACCA
CCAACCTGTACCTGGGCAGCATGGCCGTGTCCGACCTGCTCATCCTGCTCGGGCT
GCCCTTCGACCTGTACCGCCTGTGGCGCTCGAGGCCCTGGGTGTTCGGACAGCTG
CTCTGCCGCCTGTCGCTGTACGTGGGCGAGGGCTGCACCTACGCCTCGCTGCTGC
ACATGACGGCGCTCAGCGTGGAGCGCTACCTGGCCATCTGCCGCCCGCTGCGTG
CCCGCGTCTTGGTCACCCGCCGCCGGGTCCGCGCGCTCATCGCCGCGCTCTGGGC
CGTGGCGCTGCTTTCGGCCGGGCCCTTCTTCTTTCTGGTGGGCGTCGAGCAGGAC
CCCGCGGTCTTCGCGGCCCCGGACCGCAACGGTACTGTGCCGCTGGACCCCTCGT
CGCCCGCCCCGGCGTCCCCGCCGTCGGGGCCCGGAGCGGAGGCCGCGGCTCTGT
TCAGCCGCGAGTGCCGGCCGAGCCGCGCGCAGCTGGGCTTGCTGCGCGTCATGC
TGTGGGTTACCACCGCCTACTTTTTCCTGCCCTTCCTCTGCCTCAGCATCCTCTAC
GGGCTCATCGCGCGGCAGCTGTGGCGGGGTCGGGGCCCGCTGCGAGGCCCGGCG
GCCACGGGTCGGGAGAGGGGCCACCGGCAGACCGTCCGCGTCCTGCTGGTGGTG
GTTCTGGCCTTTATAGTGTGCTGGCTGCCTTTCCACGTTGGCAGGATCATTTACAT
AAACACCCAAGACTCGCGGATGATGTACTTCTCCCAGTACTTTAACATTGTCGCG
CTGCAGCTTTTCTACCTGAGTGCGTCCATCAACCCAATCCTCTACAACCTCATCTC
CAAGAAGTACAGAGCGGCTGCCCGCAGACTGCTGCGCGAAAGCCGAGCGGGGC
CCAGTGGTGTGTGCGGAAGCAGGGGCCCTGAGCAGGACGTTGCAGGGGACACTG

GCGGAGACACAGCTGGCTGCACCGAGACCAGCGCTAACACAAAGACGGCTGCAT
AG

Other embodiments are within the following claims. While several embodiments have been shown and described, various modifications may be made without departing from the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A purified polypeptide comprising a unique amino acid region of SEQ. ID. NO. 1 or SEQ. ID. NO. 2 that is at least 9 contiguous amino acids in length, wherein said unique region is not present in SEQ. ID. NO. 5 or SEQ. ID. NO. 6.

2. The polypeptide of claim 1, wherein said unique region is from SEQ. ID. NO. 1.

3. The polypeptide of claim 2, wherein said unique region comprises an amino acid sequence selected from the group consisting of:
GPGNSSDGA (SEQ. ID. NO. 9);
VCLGLFAVGV (SEQ. ID. NO. 10);
ALLSSRRRA (SEQ. ID. NO. 11);
APFFFLVGVEQDAGG (SEQ. ID. NO. 12); and
CLCVLYGRI (SEQ. ID. NO. 13).

4. The polypeptide of claim 2, wherein said polypeptide comprises the amino acid sequence of SEQ. ID. NO. 1.

5. The polypeptide of claim 4, wherein said polypeptide consists of the amino acid sequence of SEQ. ID. NO. 1.

6. The polypeptide of claim 1, wherein said unique region is from SEQ. ID. NO. 2.

7. The polypeptide of claim 6, wherein said unique region comprises an amino acid sequence selected from the group consisting of:
DPAVFAAPDR (SEQ. ID. NO. 14);
NGTVPLDPS (SEQ. ID. NO. 15);
SPAPASPPSGPG (SEQ. ID. NO. 16);
RRLLRESRAG (SEQ. ID. NO. 17); and
SGVCGSRGPEQD (SEQ. ID. NO. 18).

8. The polypeptide of claim 6, wherein said polypeptide comprises the amino acid sequence of SEQ. ID. NO. 2.

9. The polypeptide of claim 8, wherein said polypeptide consists of the amino acid sequence of SEQ. ID. NO. 2.

10. A purified nucleic acid comprising a nucleotide sequence encoding for the polypeptide of any one of claims 1-9.

11. A purified nucleic acid comprising a unique nucleotide sequence region of SEQ. ID. NO. 3 or SEQ. ID. NO. 4 that is at least 18 contiguous nucleotides in length or the complement thereof, wherein said unique region is not present in SEQ. ID. NO. 7 or SEQ. ID. NO. 8.

12. The purified nucleic acid of claim 11, wherein said unique sequence region is from SEQ. ID. NO. 3.

13. The purified nucleic acid of claim 12, wherein said unique region comprises a nucleotide sequence selected from the group consisting of:
GGCCCCGGGAACAGCAGCGACGGCGCG (SEQ. ID. NO. 19);
GGCCGTGTGCCTGGGCCT (SEQ. ID. NO. 20);
CGCGCGCTGCTGTCCCGG (SEQ. ID. NO. 21);
AGGACGCGGGCGGCCCCG (SEQ. ID. NO. 22); and
CCGCGAGCTGCGGAGGCG (SEQ. ID. NO. 23).

14. The purified nucleic acid of claim 12, wherein said nucleic acid comprises the nucleotide sequence of SEQ. ID. NO. 3.

15. The purified nucleic acid of claim 14, wherein said nucleic acid consists of the nucleotide sequence of SEQ. ID. NO. 3.

16. The purified nucleic acid of claim 11, wherein said unique sequence region is from SEQ. ID. NO. 4.

17. The purified nucleic acid of claim 16, wherein said unique region comprises a sequence selected from the group consisting of:
TTCGGCCGGGCCCTTCTTCTTT (SEQ. ID. NO. 24);
GGTCTTCGCGGCCCCGGA (SEQ. ID. NO. 25);
CGGTACTGTGCCGCTGGA (SEQ. ID. NO. 26);
GCTTTTCTACCTGAGTGCGTCC (SEQ. ID. NO. 27); and
CGAGCGGGGCCCAGTGGTG (SEQ. ID. NO. 28).

18. The purified nucleic acid of claim 16, wherein said nucleic acid comprises the nucleotide sequence of SEQ. ID. NO. 4.

19. The purified nucleic acid of claim 18, wherein said nucleic acid consists of the nucleotide sequence of SEQ. ID. NO. 4.

20. An expression vector comprising a recombinant nucleotide sequence encoding for a unique amino acid region of SEQ. ID. NO. 1 or SEQ. ID. NO. 2 that is at least 9 contiguous amino acids in length, wherein said unique region is not present in SEQ. ID. NO. 5 or SEQ. ID. NO. 6.

21. A recombinant cell comprising an expression vector encoding for a unique amino acid region of SEQ. ID. NO. 1 or SEQ. ID. NO. 2, that is at least 9 contiguous amino acids in length, functionally coupled to a promoter recognized by said cell, wherein said unique region is not present in SEQ. ID. NO. 5 or SEQ. ID. NO. 6.

22. A recombinant cell made by a process comprising the step of introducing into said cell an expression vector encoding for a unique amino acid region of SEQ. ID. NO. 1 or SEQ. ID. NO. 2, that is at least 9 contiguous amino acids in length wherein said unique region is not present in SEQ. ID. NO. 5 or 6.

23. A method of measuring the ability of a compound to effect motilin receptor activity comprising the steps of:

a) contacting a recombinant cell with said compound, wherein said recombinant cell comprises a recombinant nucleic acid expressing a functional motilin receptor that comprises a unique amino acid region of SEQ. ID. NO. 1 or SEQ. ID. NO. 2

that is at least 9 contiguous amino acids in length, provided that said unique region is not present in SEQ. ID. NO. 5 or 6; and

b) measuring motilin receptor activity.

24. A method of preparing a motilin receptor polypeptide comprising the step of growing the recombinant cell of claim 21 under conditions wherein said polypeptide is expressed from said expression vector.

```
                1                                                   50
huMTLr          MGSPWNGSDG PEGAREPPWP ALPPCDERRC SPFPLGALVP VTAVCLCLFV
dogMTLr         MGGPGNSSDG AEGAQ..... .LP.CDERLC SPFPLGALVP VTAVCLGLFA
rabMTLr         MGSPWNGSDG PEDAREPPWA ALPPCDERRC SPFPLGTLVP VTAVCLGLFA
fish75e7        MPWTRPQVDL HAAAAETMDQ YTTDDHHYEG SLFPASTLIP VTVICILIFV

               51                                                  100
huMTLr          VGVSGNVVTV MLIGRYRDMR TTTNLYLGSM AVSDLLILLG LPFDLYRLWR
dogMTLr         VGVSGNLVTV LLIGRYRDMR TTTNLYLGSM AVSDLLILLG LPLDLYRLWR
rabMTLr         VGVSGNVVTV LLIGRYRDMR TTTNLYLGSM AVSDLLILLG LPFDLYRLWR
fish75e7        VGVTGNTMTI LIIQYFKDMK TTTNLYLSSM AVSDLVIFLC LPFDLYRLWK

               101                                                 150
huMTLr          SRPWVFGPLL CRLSLYVGEG CTYATLLHMT ALSVERYLAI CRPLRARVLV
dogMTLr         SRPWVFGQLL CRLSLYLGEG CTYATLLHVT ALSVERYLAV CRPLRARALL
rabMTLr         SRPWVFGQLL CRLSLYVGEG CTYASLLHMT ALSVERYLAI CRPLRARVLV
fish75e7        YVPWLFGEAV CRLYHYIFEG CTSATILHIT ALSIERYLAI SFPLRSKVMV

               151                                                 200
huMTLr          TRRRVRALIA VLWAVALLSA GPFLFLVGVE QDPGISVVPG LNGTARIASS
dogMTLr         SRRRARALIA ALWAVALLSA APFFFLVGVE QDAGG...PG LNGSARLA..
rabMTLr         TRRRVRALIA ALWAVALLSA GPFFFLVGVE QDPAVFAAPD RNGTVPLDPS
fish75e7        TRRRVQYIIL ALWCFALVSA APTLFLVGVE YDNET..HPD YN........

               201                                                 250
huMTLr          PLASSPPLWL SRAPPPSPPS GPETAEAAAL FSRECRPSPA QLGALRVMLW
dogMTLr         .......... .RAP..SPPP GPE....AAL FSRECRPSPS QLGALRVMLW
rabMTLr         .......... SPAP.ASPPS GPG.AEAAAL FSRECRPSRA QLGLLRVMLW
fish75e7        .......... .........T GQCKHTGYAI SS........ ..GQLHIMIW

               251                                                 300
huMTLr          VTTAYFFLPF LCLSILYGLI GRELWSSRRP LRGPAASGRE RGHRQTVRVL
dogMTLr         VTTAYFFLPF LCLCVLYGRI GRELRRRRGP LRGRAASGRE RGHRQAVRVL
rabMTLr         VTTAYFFLPF LCLSILYGLI ARQLWRGRGP LRGPAATGRE RGHRQTVRVL
fish75e7        VSTTYFFCPM LCLLFLYGSI GCKLWKSKND LQGPCALARE RSHRQTVKIL

               301                                                 350
huMTLr          LVVVLAFIIC WLPFHVGRII YINTEDSRMM YFSQYFNIVA LQLFYLSASI
dogMTLr         .......... .......... .......... .......... ..........
rabMTLr         LVVVLAFIVC WLPFHVGRII YINTQDSRMM YFSQYFNIVA LQLFYLSASI
fish75e7        VVVVLAFIIC WLPYHIGRNL FAQVDDYDTA MLSQNFNMAS MVLCYLSASI

               351                                                 400
huMTLr          NPILYNLISK KYRAAAFKLL LARKSRPRGF HRSRDTAGEV AGDTGGDTVG
dogMTLr         .......... .......... .......... .......... ..........
rabMTLr         NPILYNLISK KYRAAARRLL RESRAGPSGV CGSRGPEQDV AGDTGGDTAG
fish75e7        NPVVYNLMSR KYRAAAKRLF LLHQ.RPKPA HR........ .GQGQFCMIG

               401      412
huMTLr          YTETSANVKT MG      (SEQ. ID. NO. 6)
dogMTLr         .......... ..      (SEQ. ID. NO. 1)
rabMTLr         CTETSANTKT AA      (SEQ. ID. NO. 2)
fish75e7        HSPTLDESLT GV      (SEQ. ID. NO. 5)
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FIG. 1

```
            1                                                   50
rabMTLr     ATGGGCAGCC CCTGGAACGG CAGCGACGGC CCCGAGGACG CGCGGGAGCC
huMTLr      ATGGGCAGCC CCTGGAACGG CAGCGACGGC CCCGAGGGGG CGCGGGAGCC
dogMTLr     ATGGGCGGCC CCGGGAACAG CAGCGACGGC GCGGAGGGCG CGC...AG..
fish75e7    ATGCCCTGGA CCAG..ACCC CAGGTGGACC TCCATGCTGC TGCAGCAGAG

            51                                                  100
rabMTLr     GCCGTGGGCC GCGCTGCCGC CGTGCGATGA GCGCCGCT.. ....GCTCGC
huMTLr      GCCGTGGCCC GCGCTGCCGC CTTGCGACGA GCGCCGCT.. ....GCTCGC
dogMTLr     ........C. .......TGC CGTGCGACGA GCGCCTGT.. ....GCTCGC
fish75e7    ACCATGGACC AGTA...CAC CACG.GACGA CCACCACTAC GAGGGCTCCC

            101                                                 150
rabMTLr     CCTTCCCCTT GGGCACGCTG GTGCCTGTGA CGGCCGTGTG CCTGGGCCTG
huMTLr      CCTTTCCCCT GGGGGCGCTG GTGCCGGTGA CCGCTGTGTG CCTGTGCCTG
dogMTLr     CCTTCCCCCT GGGGGCGCTG GTGCCGGTGA CGGCCGTGTG CCTGGGCCTG
fish75e7    TCTTCCCCGC GTCCACCCTC ATCCCCGTCA CGGTCATCTG CATCCTCATC

            151                                                 200
rabMTLr     TTCGCCGTCG GGGTGAGCGG CAACGTGGTG ACCGTGCTGC TGATCGGGCG
huMTLr      TTCGTCGTCG GGGTGAGCGG CAACGTGGTG ACCGTGATGC TGATCGGGCG
dogMTLr     TTCGCCGTCG GCGTGAGCGG CAACCTGGTG ACGGTGCTGC TGATCGGCCG
fish75e7    TTCGTGGTCG GCGTGACCGG CAACACCATG ACCATCCTCA TCATCCAGTA

            201                                                 250
rabMTLr     CTACCGGGAC ATGCGGACCA CCACCAACCT GTACCTGGGC AGCATGGCCG
huMTLr      CTACCGGGAC ATGCGGACCA CCACCAACTT GTACCTGGGC AGCATGGCCG
dogMTLr     CTACCGCGAC ATGCGCACCA CCACCAACCT GTACCTGGGC AGCATGGCCG
fish75e7    CTTCAAGGAC ATGAAGACCA CCACCAACCT GTACCTGTCC AGCATGGCCG

            251                                                 300
rabMTLr     TGTCCGACCT GCTCATCCTG CTCGGGCTGC CCTTCGACCT GTACCGCCTG
huMTLr      TGTCCGACCT ACTCATCCTG CTCGGGCTGC CGTTCGACCT GTACCGCCTC
dogMTLr     TGTCCGACCT GCTCATCCTG CTGGGGCTGC CCCTCGACCT GTACCGCCTG
fish75e7    TGTCCGACCT CGTCATCTTC CTCTGCCTGC CCTTCGACCT GTACCGCCTG

            301                                                 350
rabMTLr     TGGCGCTCGA GGCCCTGGGT GTTCGGACAG CTGCTCTGCC GCCTGTCGCT
huMTLr      TGGCGCTCGC GGCCCTGGGT GTTCGGGCCG CTGCTCTGCC GCCTGTCCCT
dogMTLr     TGGCGCTCGC GGCCCTGGGT GTTCGGGCAG CTGCTGTGCC GCCTGTCGCT
fish75e7    TGGAAGTACG TGCCGTGGCT GTTCGGCGAG GCCGTGTGCC GCCTCTACCA

            351                                                 400
rabMTLr     GTACGTGGGC GAGGGCTGCA CCTACGCCTC GCTGCTGCAC ATGACGGCGC
huMTLr      CTACGTGGGC GAGGGCTGCA CCTACGCCAC GCTGCTGCAC ATGACCGCGC
dogMTLr     GTACCTGGGC GAGGGCTGCA CCTACGCCAC GCTGCTGCAC GTGACGGCGC
fish75e7    CTACATCTTC GAAGGCTGCA CGTCGGCCAC CATCCTCCAC ATCACGGCCC

            401                                                 450
rabMTLr     TCAGCGTGGA GCGCTACCTG GCCATCTGCC GCCCGCTGCG TGCCCGCGTC
huMTLr      TCAGCGTCGA GCGCTACCTG GCCATCTGCC GCCCGCTCCG CGCCCGCGTC
dogMTLr     TGAGCGTCGA GCGCTACCTG GCCGTGTGCC GCCCGCTCCG CGCCCGCGCG
fish75e7    TGAGCATCGA GCGCTACCTG GCCATCAGCT TCCCCCTCAG GAGCAAGGTG
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FIG. 2A

```
          451                                                        500
rabMTLr   TTGGTCACCC GCCGCCGGGT CCGCGCGCTC ATCGCCGCGC TCTGGGCCGT
huMTLr    TTGGTCACCC GGCGCCGCGT CCGCGCGCTC ATCGCTGTGC TCTGGGCCGT
dogMTLr   CTGCTGTCCC GGCGCCGCGC CCGCGCGCTC ATCGCGGCGC TCTGGGCCGT
fish75e7  ATGGTGACCA GGAGAAGGGT CCAGTACATC ATCCTGGCCC TGTGGTGCTT

          501                                                        550
rabMTLr   GGCGCTGCTT TCGGCCGGGC CCTTCTTCTT TCTGGTGGGC GTCGAGCAGG
huMTLr    GGCGCTGCTC TCTGCCGGTC CCTTCTTGTT CCTGGTGGGC GTCGAGCAGG
dogMTLr   GGCGCTGCTG TCGGCCGCGC CCTTCTTCTT CCTGGTGGGC GTCGAGCAGG
fish75e7  CGCCCTGGTG TCGGCCGCTC CCACGCTCTT CCTGGTCGGG GTGGAGTACG

          551                                                        600
rabMTLr   ACCCCGCGGT CTTCGCGGCC CCGGACCGCA ACGGTACTGT GCCGCTGGAC
huMTLr    ACCCCGGCAT CTCCGTAGTC CCGGGCCTCA ATGGCACCGC GCGGATCGCC
dogMTLr   ACGCGG.... ....GCGGCC CCGG.CCTCA ACGGCAGCGC GCGGCTGG..
fish75e7  ACAACG.... ......AGAC GCA..CCCCG ACTACAACAC G.GG......

          601                                                        650
rabMTLr   CCCTCGTCGC CCGCC..... .......... .......... ........CC
huMTLr    TCCTCGCCTC TCGCCTCGTC GCCGCCTCTC TGGCTCTCGC GGGCGCCACC
dogMTLr   .........C GCGGG..... .......... .......... .........C
fish75e7  .......... .......... .......... .......... ..........

          651                                                        700
rabMTLr   GGCGTCCCCG CCGTCGGGGC CCGGA...GC GGAGGCCGCG GCTCTGTTCA
huMTLr    GCCGTCCCCG CCGTCGGGGC CCGAGACCGC GGAGGCCGCG GCGCTGTTCA
dogMTLr   GCCCTCCCCG CCGCCGGGGC CCGAG..... ....G...CG GCGCTCTTCA
fish75e7  .......... .........C CAGTG..... .......... ..........

          701                                                        750
rabMTLr   GCCGCGAGTG CCGGCCGAGC CGCGCGCAGC TGGGCTT.GC TGCGCGTCAT
huMTLr    GCCGCGAATG CCGGCCGAGC CCCGCGCAGC TGGGCGC.GC TGCGTGTCAT
dogMTLr   GCCGGGAGTG CCGGCCCAGC CCGTCGCAGC TGGGCGC.GC TGCGCGTCAT
fish75e7  ..CAAGCACA CGGGCTACGC CAT...CAGC TCGGGGCAGC TGCACATCAT

          751                                                        800
rabMTLr   GCTGTGGGTT ACCACCGCCT ACTTTTTCCT GCCCTTCCTC TGCCTCAGCA
huMTLr    GCTGTGGGTC ACCACCGCCT ACTTCTTCCT GCCCTTTCTG TGCCTCAGCA
dogMTLr   GCTCTGGGTC ACCACCGCCT ACTTCTTCCT GCCCTTCCTG TGCCTCTGCG
fish75e7  GATCTGGGTG TCCACCACCT ACTTCTTCTG CCCGATGCTG TGTCTCCTCT

          801                                                        850
rabMTLr   TCCTCTACGG GCTCATCGCG CGGCAGCTGT GGCGGGGTCG GGGCCCGCTG
huMTLr    TCCTCTACGG GCTCATCGGG CGGGAGCTGT GGAGCAGCCG GCGGCCGCTG
dogMTLr   TCCTGTACGG GCGCATCGGC CGCGAGCTGC GGAGGCGCCG GGGGCCGCTG
fish75e7  TCCTCTACGG CTCCATCGGG TGCAAGCTGT GGAAGAGCAA GAACGACCTG
```

FIG. 2B

```
            851                                                   900
rabMTLr     CGAGGCCCGG CGGCCACGGG TCGGGAGAGG GGCCACCGGC AGACCGTCCG
huMTLr      CGAGGCCCGG CCGCCTCGGG GCGGGAGAGA GGCCACCGGC AGACCGTCCG
dogMTLr     CGGGGCCGGG CCGCCTCGGG GCGCGAGCGG GGCCACCGCC AGGCCGTCCG
fish75e7    CAGGGCCCGT GCGCCCTGGC CCGCGAGAGG TCGCACAGGC AAACGGTGAA

            901                                                   950
rabMTLr     CGTCCTGCTG GTGGTGGTTC TGGCCTTTAT AGTGTGCTGG CTGCCTTTCC
huMTLr      CGTCCTGCTG GTGGTGGTTC TGGCATTTAT AATTTGCTGG TTGCCCTTCC
dogMTLr     CGTGCTG... .......... .......... .......... ..........
fish75e7    GATCCTGGTG GTGGTGGTGC TGGCCTTCAT CATCTGCTGG CTGCCCTACC

            951                                                  1000
rabMTLr     ACGTTGGCAG GATCATTTAC ATAAACACCC AAGACTCGCG GATGATGTAC
huMTLr      ACGTTGGCAG AATCATTTAC ATAAACACGG AAGATTCGCG GATGATGTAC
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    ACATCGGCAG GAACCTGTTC GCCCAGGTGG ACGACTACGA CACGGCCATG


            1001                                                 1050
rabMTLr     TTCTCCCAGT ACTTTAACAT TGTCGCGCTG CAGCTTTTCT ACCTGAGTGC
huMTLr      TTCTCTCAGT ACTTTAACAT CGTCGCTCTG CAACTTTTCT ATCTGAGCGC
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    CTCAGCCAGA ATTTCAACAT GGCCTCCATG GTGCTCTGCT ACCTCAGCGC

            1051                                                 1100
rabMTLr     GTCCATCAAC CCAATCCTCT ACAACCTCAT CTCCAAGAAG TACAGAGCGG
huMTLr      ATCTATCAAC CCAATCCTCT ACAACCTCAT TTCAAAGAAG TACAGAGCGG
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    CTCCATCAAC CCCGTCGTCT ACAACCTGAT GTCGAGGAAG TACCGGGCCG

            1101                                                 1150
rabMTLr     CTGCC...CG CAGACTGCTG CGCGAAAGCC GAGCGGGGCC CAGTGGTGTG
huMTLr      CGGCC...TT TAAACTGCTG CTCGCAAGGA AGTCCAGGCC GAGAGGCTTC
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    CCGCCAAGCG CCTCTTCCTG CTCCACCAGA GACCCAAGCC ..GGCCCACC

            1151                                                 1200
rabMTLr     TGCGGAAGCA GGGGCCCTGA GCAGGACGTT GCAGGGG.AC ACTGGCGGAG
huMTLr      CACAGAAGCA GGGACACTGC GGGGGAAGTT GCAGGGG.AC ACTGGAGGAG
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    GGGGGCAGGG GCAGTTTTGC ATGATCGGCC ACAGCCCCAC CCTGGACGAG

            1201                                                 1250
rabMTLr     ACACAGCTGG CTGCACCGAG ACCAGCGCTA ACACAAAGAC GGCTGCATAG
huMTLr      ACACGGTGGG CTACACCGAG ACAAGCGCTA ACGTGAAGAC GATGGGATAA
dogMTLr     .......... .......... .......... .......... ..........
fish75e7    AGCCTGACGG GGGTGTGA.. .......... .......... ..........

rabMTLr     (SEQ. ID. NO. 4)
huMTLr      (SEQ. ID. NO. 7)
dogMTLr     (SEQ. ID. NO. 3)
fish75e7    (SEQ. ID. NO. 8)
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FIG. 2C

SEQUENCE LISTING

<110> Merck & Co., Inc.

<120> DOG AND RABBIT MOTILIN RECEPTOR ORTHOLOGS

<130> PCT 20390

<150> 60/162,264
<151> 1999-10-29

<160> 32

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 271
<212> PRT
<213> Dog

<400> 1

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            20                  25                  30
Pro Val Thr Ala Val Cys Leu Gly Leu Phe Ala Val Gly Val Ser Gly
        35                  40                  45
Asn Leu Val Thr Val Leu Leu Ile Gly Arg Tyr Arg Asp Met Arg Thr
    50                  55                  60
Thr Thr Asn Leu Tyr Leu Gly Ser Met Ala Val Ser Asp Leu Leu Ile
65                  70                  75                  80
Leu Leu Gly Leu Pro Leu Asp Leu Tyr Arg Leu Trp Arg Ser Arg Pro
                85                  90                  95
Trp Val Phe Gly Gln Leu Leu Cys Arg Leu Ser Leu Tyr Leu Gly Glu
            100                 105                 110
Gly Cys Thr Tyr Ala Thr Leu Leu His Val Thr Ala Leu Ser Val Glu
        115                 120                 125
Arg Tyr Leu Ala Val Cys Arg Pro Leu Arg Ala Arg Ala Leu Leu Ser
    130                 135                 140
Arg Arg Arg Ala Arg Ala Leu Ile Ala Ala Leu Trp Ala Val Ala Leu
145                 150                 155                 160
Leu Ser Ala Ala Pro Phe Phe Phe Leu Val Gly Val Glu Gln Asp Ala
                165                 170                 175
Gly Gly Pro Gly Leu Asn Gly Ser Ala Arg Leu Ala Arg Ala Pro Ser
            180                 185                 190
Pro Pro Pro Gly Pro Glu Ala Ala Leu Phe Ser Arg Glu Cys Arg Pro
        195                 200                 205
Ser Pro Ser Gln Leu Gly Ala Leu Arg Val Met Leu Trp Val Thr Thr
    210                 215                 220
Ala Tyr Phe Phe Leu Pro Phe Leu Cys Leu Cys Val Leu Tyr Gly Arg
225                 230                 235                 240
Ile Gly Arg Glu Leu Arg Arg Arg Arg Gly Pro Leu Arg Gly Arg Ala
                245                 250                 255
Ala Ser Gly Arg Glu Arg Gly His Arg Gln Ala Val Arg Val Leu
            260                 265                 270
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<210> 2
<211> 400
<212> PRT
<213> Rabbit

<400> 2
Met Gly Ser Pro Trp Asn Gly Ser Asp Gly Pro Glu Asp Ala Arg Glu
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Pro Pro Trp Ala Ala Leu Pro Pro Cys Asp Glu Arg Arg Cys Ser Pro
20 25 30
Phe Pro Leu Gly Thr Leu Val Pro Val Thr Ala Val Cys Leu Gly Leu
35 40 45
Phe Ala Val Gly Val Ser Gly Asn Val Val Thr Val Leu Leu Ile Gly
50 55 60
Arg Tyr Arg Asp Met Arg Thr Thr Thr Asn Leu Tyr Leu Gly Ser Met
65 70 75 80
Ala Val Ser Asp Leu Leu Ile Leu Leu Gly Leu Pro Phe Asp Leu Tyr
85 90 95
Arg Leu Trp Arg Ser Arg Pro Trp Val Phe Gly Gln Leu Leu Cys Arg
100 105 110
Leu Ser Leu Tyr Val Gly Glu Gly Cys Thr Tyr Ala Ser Leu Leu His
115 120 125
Met Thr Ala Leu Ser Val Glu Arg Tyr Leu Ala Ile Cys Arg Pro Leu
130 135 140
Arg Ala Arg Val Leu Val Thr Arg Arg Arg Val Arg Ala Leu Ile Ala
145 150 155 160
Ala Leu Trp Ala Val Ala Leu Leu Ser Ala Gly Pro Phe Phe Phe Leu
165 170 175
Val Gly Val Glu Gln Asp Pro Ala Val Phe Ala Ala Pro Asp Arg Asn
180 185 190
Gly Thr Val Pro Leu Asp Pro Ser Ser Pro Ala Pro Ala Ser Pro Pro
195 200 205
Ser Gly Pro Gly Ala Glu Ala Ala Ala Leu Phe Ser Arg Glu Cys Arg
210 215 220
Pro Ser Arg Ala Gln Leu Gly Leu Leu Arg Val Met Leu Trp Val Thr
225 230 235 240
Thr Ala Tyr Phe Phe Leu Pro Phe Leu Cys Leu Ser Ile Leu Tyr Gly
245 250 255
Leu Ile Ala Arg Gln Leu Trp Arg Gly Arg Gly Pro Leu Arg Gly Pro
260 265 270
Ala Ala Thr Gly Arg Glu Arg Gly His Arg Gln Thr Val Arg Val Leu
275 280 285
Leu Val Val Val Leu Ala Phe Ile Val Cys Trp Leu Pro Phe His Val
290 295 300
Gly Arg Ile Ile Tyr Ile Asn Thr Gln Asp Ser Arg Met Met Tyr Phe
305 310 315 320
Ser Gln Tyr Phe Asn Ile Val Ala Leu Gln Leu Phe Tyr Leu Ser Ala
325 330 335
Ser Ile Asn Pro Ile Leu Tyr Asn Leu Ile Ser Lys Lys Tyr Arg Ala
340 345 350
Ala Ala Arg Arg Leu Leu Arg Glu Ser Arg Ala Gly Pro Ser Gly Val
355 360 365
Cys Gly Ser Arg Gly Pro Glu Gln Asp Val Ala Gly Asp Thr Gly Gly
370 375 380
Asp Thr Ala Gly Cys Thr Glu Thr Ser Ala Asn Thr Lys Thr Ala Ala
385 390 395 400

<210> 3
<211> 813
<212> DNA
<213> Dog

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cgcctgtgct cgcccttccc cctgggggcg ctggtgccgg tgacggccgt gtgcctgggc 120
ctgttcgccg tcggcgtgag cggcaacctg gtgacggtgc tgctgatcgg ccgctaccgc 180
gacatgcgca ccaccaccaa cctgtacctg ggcagcatgg ccgtgtccga cctgctcatc 240

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ctgctggggc tgcccctcga cctgtaccgc ctgtggcgct cgcggccctg ggtgttcggg     300
cagctgctgt gccgcctgtc gctgtacctg ggcgagggct gcacctacgc cacgctgctg     360
cacgtgacgg cgctgagcgt cgagcgctac ctggccgtgt gccgcccgct ccgcgcccgc     420
gcgctgctgt cccggcgccg cgcccgcgcg ctcatcgcgg cgctctgggc cgtggcgctg     480
ctgtcggccg cgcccttctt cttcctggtg ggcgtcgagc aggacgcggg cggccccggc     540
ctcaacggca gcgcgcggct ggcgcgggcg ccctccccgc cgccggggcc cgaggcggcg     600
ctcttcagcc gggagtgccg gcccagcccg tcgcagctgg gcgcgctgcg cgtcatgctc     660
tgggtcacca ccgcctactt cttcctgccc ttcctgtgcc tctgcgtcct gtacgggcgc     720
atcggccgcg agctgcggag gcgccggggg ccgctgcggg gccgggccgc ctcggggcgc     780
gagcggggcc accgccaggc cgtccgcgtg ctg                                  813

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<211> 1203
<212> DNA
<213> Rabbit

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gcgctgccgc cgtgcgatga gcgccgctgc tcgcccttcc ccttgggcac gctggtgcct     120
gtgacggccg tgtgcctggg cctgttcgcc gtcggggtga gcggcaacgt ggtgaccgtg     180
ctgctgatcg ggcgctaccg ggacatgcgg accaccacca acctgtacct gggcagcatg     240
gccgtgtccg acctgctcat cctgctcggg ctgcccttcg acctgtaccg cctgtggcgc     300
tcgaggccct gggtgttcgg acagctgctc tgccgcctgt cgctgtacgt gggcgagggc     360
tgcacctacg cctcgctgct gcacatgacg gcgctcagcg tggagcgcta cctggccatc     420
tgccgcccgc tgcgtgcccg cgtcttggtc acccgccgcc gggtccgcgc gctcatcgcc     480
gcgctctggg ccgtggcgct gctttcggcc gggcccttct tctttctggt gggcgtcgag     540
caggaccccg cggtcttcgc ggccccggac cgcaacggta ctgtgccgct ggaccccctcg     600
tcgcccgccc cggcgtcccc gccgtcgggg cccggagcgg aggccgcggc tctgttcagc     660
cgcgagtgcc ggccgagccg cgcgcagctg ggcttgctgc gcgtcatgct gtgggttacc     720
accgcctact ttttcctgcc cttcctctgc ctcagcatcc tctacgggct catcgcgcgg     780
cagctgtggc ggggtcgggg cccgctgcga ggcccggcgg ccacgggtcg ggagaggggc     840
caccggcaga ccgtccgcgt cctgctggtg gtggttctgg cctttatagt gtgctggctg     900
cctttccacg ttggcaggat catttacata aacacccaag actcgcggat gatgtacttc     960
tcccagtact ttaacattgt cgcgctgcag cttttctacc tgagtgcgtc catcaaccca    1020
atcctctaca acctcatctc caagaagtac agagcggctg cccgcagact gctgcgcgaa    1080
agccgagcgg ggcccagtgg tgtgtgcgga agcaggggcc ctgagcagga cgttgcaggg    1140
gacactggcg gagacacagc tggctgcacc gagaccagcg ctaacacaaa gacggctgca    1200
tag                                                                  1203

<210> 5
<211> 412
<212> PRT
<213> Human

<400> 5
Met Gly Ser Pro Trp Asn Gly Ser Asp Gly Pro Glu Gly Ala Arg Glu
 1               5                  10                  15
Pro Pro Trp Pro Ala Leu Pro Pro Cys Asp Glu Arg Arg Cys Ser Pro
            20                  25                  30
Phe Pro Leu Gly Ala Leu Val Pro Val Thr Ala Val Cys Leu Cys Leu
        35                  40                  45
Phe Val Val Gly Val Ser Gly Asn Val Val Thr Val Met Leu Ile Gly
    50                  55                  60
Arg Tyr Arg Asp Met Arg Thr Thr Thr Asn Leu Tyr Leu Gly Ser Met
65                  70                  75                  80
Ala Val Ser Asp Leu Leu Ile Leu Leu Gly Leu Pro Phe Asp Leu Tyr
                85                  90                  95
Arg Leu Trp Arg Ser Arg Pro Trp Val Phe Gly Pro Leu Leu Cys Arg
            100                 105                 110
Leu Ser Leu Tyr Val Gly Glu Gly Cys Thr Tyr Ala Thr Leu Leu His
        115                 120                 125
```

```
Met Thr Ala Leu Ser Val Glu Arg Tyr Leu Ala Ile Cys Arg Pro Leu
    130                 135                 140
Arg Ala Arg Val Leu Val Thr Arg Arg Arg Val Arg Ala Leu Ile Ala
145                 150                 155                 160
Val Leu Trp Ala Val Ala Leu Leu Ser Ala Gly Pro Phe Leu Phe Leu
                165                 170                 175
Val Gly Val Glu Gln Asp Pro Gly Ile Ser Val Val Pro Gly Leu Asn
            180                 185                 190
Gly Thr Ala Arg Ile Ala Ser Ser Pro Leu Ala Ser Ser Pro Pro Leu
        195                 200                 205
Trp Leu Ser Arg Ala Pro Pro Pro Ser Pro Pro Ser Gly Pro Glu Thr
    210                 215                 220
Ala Glu Ala Ala Ala Leu Phe Ser Arg Glu Cys Arg Pro Ser Pro Ala
225                 230                 235                 240
Gln Leu Gly Ala Leu Arg Val Met Leu Trp Val Thr Thr Ala Tyr Phe
                245                 250                 255
Phe Leu Pro Phe Leu Cys Leu Ser Ile Leu Tyr Gly Leu Ile Gly Arg
            260                 265                 270
Glu Leu Trp Ser Ser Arg Arg Pro Leu Arg Gly Pro Ala Ala Ser Gly
        275                 280                 285
Arg Glu Arg Gly His Arg Gln Thr Val Arg Val Leu Leu Val Val Val
    290                 295                 300
Leu Ala Phe Ile Ile Cys Trp Leu Pro Phe His Val Gly Arg Ile Ile
305                 310                 315                 320
Tyr Ile Asn Thr Glu Asp Ser Arg Met Met Tyr Phe Ser Gln Tyr Phe
                325                 330                 335
Asn Ile Val Ala Leu Gln Leu Phe Tyr Leu Ser Ala Ser Ile Asn Pro
            340                 345                 350
Ile Leu Tyr Asn Leu Ile Ser Lys Lys Tyr Arg Ala Ala Ala Phe Lys
        355                 360                 365
Leu Leu Leu Ala Arg Lys Ser Arg Pro Arg Gly Phe His Arg Ser Arg
    370                 375                 380
Asp Thr Ala Gly Glu Val Ala Gly Asp Thr Gly Gly Asp Thr Val Gly
385                 390                 395                 400
Tyr Thr Glu Thr Ser Ala Asn Val Lys Thr Met Gly
                405                 410
```

<210> 6
<211> 363
<212> PRT
<213> Spheroides Nephelus

<400> 6

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Met Pro Trp Thr Arg Pro Gln Val Asp Leu His Ala Ala Ala Ala Glu
 1               5                  10                  15
Thr Met Asp Gln Tyr Thr Thr Asp Asp His His Tyr Glu Gly Ser Leu
            20                  25                  30
Phe Pro Ala Ser Thr Leu Ile Pro Val Thr Val Ile Cys Ile Leu Ile
        35                  40                  45
Phe Val Val Gly Val Thr Gly Asn Thr Met Thr Ile Leu Ile Ile Gln
    50                  55                  60
Tyr Phe Lys Asp Met Lys Thr Thr Thr Asn Leu Tyr Leu Ser Ser Met
65                  70                  75                  80
Ala Val Ser Asp Leu Val Ile Phe Leu Cys Leu Pro Phe Asp Leu Tyr
                85                  90                  95
Arg Leu Trp Lys Tyr Val Pro Trp Leu Phe Gly Glu Ala Val Cys Arg
            100                 105                 110
Leu Tyr His Tyr Ile Phe Glu Gly Cys Thr Ser Ala Thr Ile Leu His
        115                 120                 125
Ile Thr Ala Leu Ser Ile Glu Arg Tyr Leu Ala Ile Ser Phe Pro Leu
    130                 135                 140
```

```
Arg Ser Lys Val Met Val Thr Arg Arg Arg Val Gln Tyr Ile Ile Leu
145                 150                 155                 160
Ala Leu Trp Cys Phe Ala Leu Val Ser Ala Ala Pro Thr Leu Phe Leu
                165                 170                 175
Val Gly Val Glu Tyr Asp Asn Glu Thr His Pro Asp Tyr Asn Thr Gly
            180                 185                 190
Gln Cys Lys His Thr Gly Tyr Ala Ile Ser Ser Gly Gln Leu His Ile
        195                 200                 205
Met Ile Trp Val Ser Thr Thr Tyr Phe Phe Cys Pro Met Leu Cys Leu
    210                 215                 220
Leu Phe Leu Tyr Gly Ser Ile Gly Cys Lys Leu Trp Lys Ser Lys Asn
225                 230                 235                 240
Asp Leu Gln Gly Pro Cys Ala Leu Ala Arg Glu Arg Ser His Arg Gln
                245                 250                 255
Thr Val Lys Ile Leu Val Val Val Val Leu Ala Phe Ile Ile Cys Trp
            260                 265                 270
Leu Pro Tyr His Ile Gly Arg Asn Leu Phe Ala Gln Val Asp Asp Tyr
        275                 280                 285
Asp Thr Ala Met Leu Ser Gln Asn Phe Asn Met Ala Ser Met Val Leu
    290                 295                 300
Cys Tyr Leu Ser Ala Ser Ile Asn Pro Val Val Tyr Asn Leu Met Ser
305                 310                 315                 320
Arg Lys Tyr Arg Ala Ala Ala Lys Arg Leu Phe Leu Leu His Gln Arg
                325                 330                 335
Pro Lys Pro Ala His Arg Gly Gln Gly Gln Phe Cys Met Ile Gly His
            340                 345                 350
Ser Pro Thr Leu Asp Glu Ser Leu Thr Gly Val
        355                 360
```

<210> 7
<211> 1239
<212> DNA
<213> Human

<400> 7

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gcgctgccgc cttgcgacga gcgccgctgc tcgcccttc ccctgggggc gctggtgccg     120
gtgaccgctg tgtgcctgtg cctgttcgtc gtcggggtga gcggcaacgt ggtgaccgtg     180
atgctgatcg ggcgctaccg ggacatgcgg accaccacca acttgtacct gggcagcatg     240
gccgtgtccg acctactcat cctgctcggg ctgccgttcg acctgtaccg cctctggcgc     300
tcgcggccct gggtgttcgg gccgctgctc tgccgcctgt ccctctacgt gggcgagggc     360
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tgccgcccgc tccgcgcccg cgtcttggtc acccggcgcc gcgtccgcgc gctcatcgct     480
gtgctctggg ccgtggcgct gctctctgcc ggtcccttct tgttcctggt gggcgtcgag     540
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cagctgggcg cgctgcgtgt catgctgtgg gtcaccaccg cctacttctt cctgcccttt     780
ctgtgcctca gcatcctcta cgggctcatc gggcgggagc tgtggagcag ccggcggccg     840
ctgcgaggcc cggccgcctc ggggcgggag agaggccacc ggcagaccgt ccgcgtcctg     900
ctggtggtgg ttctggcatt tataatttgc tggttgccct tccacgttgg cagaatcatt     960
tacataaaca cggaagattc gcggatgatg tacttctctc agtactttaa catcgtcgct    1020
ctgcaacttt tctatctgag cgcatctatc aacccaatcc tctacaacct catttcaaag    1080
aagtacagag cggcggcctt taaactgctg ctcgcaagga agtccaggcc gagaggcttc    1140
cacagaagca gggacactgc gggggaagtt gcaggggaca ctggaggaga cacggtgggc    1200
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<210> 8
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<212> DNA
<213> Spheroides Nephelus

<400> 8
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gtcacggtca tctgcatcct catcttcgtg gtcggcgtga ccggcaacac catgaccatc 180
ctcatcatcc agtacttcaa ggacatgaag accaccacca acctgtacct gtccagcatg 240
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tacgtgccgt ggctgttcgg cgaggccgtg tgccgcctct accactacat cttcgaaggc 360
tgcacgtcgg ccaccatcct ccacatcacg gccctgagca tcgagcgcta cctggccatc 420
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gccctgtggt gcttcgccct ggtgtcggcc gctcccacgc tcttcctggt cggggtggag 540
tacgacaacg agacgcaccc cgactacaac acgggccagt gcaagcacac gggctacgcc 600
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tccatggtgc tctgctacct cagcgcctcc atcaaccccg tcgtctacaa cctgatgtcg 960
aggaagtacc gggccgccgc caagcgcctc ttcctgctcc accagagacc caagccggcc 1020
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acgggggtgt ga 1092

<210> 9
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<212> PRT
<213> Dog

<400> 9
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1 5

<210> 10
<211> 10
<212> PRT
<213> Dog

<400> 10
Val Cys Leu Gly Leu Phe Ala Val Gly Val
1 5 10

<210> 11
<211> 9
<212> PRT
<213> Dog

<400> 11
Ala Leu Leu Ser Ser Arg Arg Arg Ala
1 5

<210> 12
<211> 15
<212> PRT
<213> Dog

<400> 12
Ala Pro Phe Phe Phe Leu Val Gly Val Glu Gln Asp Ala Gly Gly
1 5 10 15

<210> 13
<211> 9
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<213> Dog

<400> 13
Cys Leu Cys Val Leu Tyr Gly Arg Ile
1 5

<210> 14
<211> 10
<212> PRT
<213> Rabbit

<400> 14
Asp Pro Ala Val Phe Ala Ala Pro Asp Arg
1 5 10

<210> 15
<211> 9
<212> PRT
<213> Rabbit

<400> 15
Asn Gly Thr Val Pro Leu Asp Pro Ser
1 5

<210> 16
<211> 12
<212> PRT
<213> Rabbit

<400> 16
Ser Pro Ala Pro Ala Ser Pro Pro Ser Gly Pro Gly
1 5 10

<210> 17
<211> 10
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<400> 17
Arg Arg Leu Leu Arg Glu Ser Arg Ala Gly
1 5 10

<210> 18
<211> 12
<212> PRT
<213> Rabbit

<400> 18
Ser Gly Val Cys Gly Ser Arg Gly Pro Glu Gln Asp
1 5 10

<210> 19
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<212> DNA
<213> Dog

<400> 19
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<210> 20
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<212> DNA
<213> Dog

<400> 20
ggccgtgtgc ctgggcct 18

<210> 21
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<212> DNA
<213> Dog

<400> 21
cgcgcgctgc tgtcccgg 18

<210> 22
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<212> DNA
<213> Dog

<400> 22
aggacgcggg cggccccg 18

<210> 23
<211> 18
<212> DNA
<213> Dog

<400> 23
ccgcgagctg cggaggcg 18

<210> 24
<211> 22
<212> DNA
<213> Rabbit

<400> 24
ttcggccggg cccttcttct tt 22

<210> 25
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<212> DNA
<213> Rabbit

<400> 25
ggtcttcgcg gccccgga 18

<210> 26
<211> 18
<212> DNA
<213> Rabbit

<400> 26
cggtactgtg ccgctgga 18

<210> 27
<211> 22
<212> DNA
<213> Rabbit

<400> 27
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<210> 28
<211> 19
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<213> Rabbit

<400> 28
cgagcggggc ccagtggtg 19

<210> 29
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<212> DNA
<213> Artificial Sequence

<220>
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<210> 30
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<210> 31
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<220>
<223> PCR Primer

<400> 31
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<210> 32
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
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<400> 32
agtttagcgg ccgcctatgc agccgtcttt gtgttagc 38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/29426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07K 14/72; C07H 21/04; C12N 15/00, 63, 85, 86; G01N 33/53
US CL :530/300; 536/23.5; 435/7.1, 69.1, 320.1, 325

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300; 536/23.5; 435/7.1, 69.1, 320.1, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE
search terms: motilin receptor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAHAIRAS et al. Sequence-tagged connectors: A sequence approach to mapping and scanning the human genome. Proc. Natl. Acad. Sci. USA, August 1999, Vol. 96, pages 9739-9744, see the abstract.	10
X	Nucleotide Database on PubMed, US National Library of Medicine, Bethesda, MD, USA), Accession No. AQ302307, MAHAIRAS et al. 'Sequence-tagged connectors: A sequence approach to mapping and scanning the human genome', 16 December 1998, see the complement of nucleotides 41 to 67.	10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 JANUARY 2001	Date of mailing of the international search report 08FEB 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorothea Laurence Lee DAVID S. ROMEO Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998) ★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/29426

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZAHRAOUI et al. Nucleotide sequence of the chicken proto-oncogene c-erbA corresponding to domain 1 of v-erbA. Eur. J. Biochem. 1987, Vol. 166, pages 63-69, see the complement of nucleotides 705-725 of the sequence in Figure 2B.	11, 12
A	WO 99/64436 A1 (MERCK & CO., INC.) 16 December 1999 (16.12.99), Claim 3, Figure 3.	1-5, 10-15, 20-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/29426

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, 10-15, 20-24

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/29426

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-5, 10-15, 20-24, to the extent that they are drawn to or encompass a polypeptide comprising and a polynucleotide encoding SEQ ID NO: 1.
Group II, claim(s) 1, 6-11, 16-24, to the extent that they are drawn to a polypeptide comprising and a polynucleotide encoding SEQ ID NO: 2.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of group I is a rabbit motilin receptor. The special technical feature of group II is a dog motilin receptor. Each of the special technical features is a structurally and functionally different chemical compound each of which can be made and used without the other. Lack of unity is shown because these compounds lack a common utility which is based upon a common structural feature which has been identified as the basis for that common utility.